II. Rejection of Claims 7, 15-17 and 37-38 under 35 U.S.C. §112(1)

The Office Action rejected claims 7, 15-17 and 37-38 under 35 U.S.C. § 112, first paragraph.

The Office Action rejected claims 7,15-17 and 37-38 on the basis that these claims contain subject matter which is not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention without undue experimentation. All elements or subsidiary parts of the Office Action are so directed to making this alleged *prima facie* case that the claims are not enabled by the specification.

The Office Action states that the November 5, 2001 and March 27, 2002 Longhurst declarations are stated to be insufficient to overcome the § 112(1) rejection because the declarant "Dr. Longhurst has not worked with any botulinum toxins."(page 4 of the Office Action). Hence, the Office Action states that the Longhurst declarations are not persuasive.

Specifically, the Office Action again applies the Johnson reference to indicate alleged complications with the use of a botulinum toxin, again asserts that the Examples set forth in the application are insufficient to enable the claimed invention, again asserts that undue experimentation would be required to practise the claimed invention, and again asserts that there is a contradictory state of the prior art.

Applicant addressed the very same rejections by the Office Action in his response to the previous office action.

Applicant believes that all the bases expressed by the Office Action to support the § 112(1) rejection made by the Office Action have been refuted by

the evidence presented by the applicant. Thus while applicant appreciates the through and extensive analysis provided by the Office Action, applicant believes that the § 112(1) rejection by the Office Action is based entirely upon the examiner's interpretation and view of the nature of the prior art and the scope of the specification. Contrarily, applicant has presented evidence in the form of two declarations from an expert cardiologist to refute this lack of enablement rejection. Surprisingly, the Office Action dismissed the November 5, 2001 and March 27, 2002 Longhurst declarations on the basis that "Dr. Longhurst has not worked with any botulinum toxins" (page 4 of the Office Action). The Office Action has therefore dismissed the expert opinion and fact evidence presented by the Longhurst declarations (i.e. "In my opinion this patent application provides sufficient disclosure and teaching so that a cardiologist of ordinary skill can successfully treat bradycardia by administration of a botulinum toxin into an existing pericardial space of a human patient (i.e. in the presence of a pericardial effusion of sufficient magnitude to allow access to the pericardial space) to thereby increase the heart rate of a patient with symptomatic bradycardia " (paragraph 6 of the November 5,2001 Longhurst declaration, and paragraph 1 of the March 27, 2002 Longhurst declaration)), by substituting the opinion of the examiner ("...the skilled artisan cannot predict that intrapericardial injection of a botulinum toxin into the SA or AV node of the heart of a patient will produce the desired response, i.e. an increased heart rate..." (page 4 of the Office Action)) for the expert opinion of the declarant.

Respectfully, this is not an appropriate basis upon which to reject the claimed invention. But rather than argue this point again and so as to advance the prosecution of this application and to directly address the basis upon which the Office Action has rejected the Longhurst declarations ("Dr. Longhurst has not worked with any botulinum toxins" (page 4 of the Office Action) applicant presents herein a February 14, 2003 declaration from Dr. Mitchell Brin the foremost authority on the therapeutic use of botulinum toxin.

Thus, the Brin declaration states that after carefully and thoroughly reading the present patent application it is Dr. Brin's expert opinion that "...this patent application provides sufficient disclosure and teaching so that a physician of ordinary skill can successfully treat bradycardia by intrapericardial injection of a botulinum toxin to the heart of a patient with bradycardia, to thereby increase the heart rate of a patient with bradycardia." (paragraph 13 of the Brin declaration). Dr. Brin explains the scientific basis for this conclusion in paragraph 14 of his declaration.

Additionally, paragraph 16 of the Brin declaration states "...in my opinion matters such as the specific time period in which the toxin should be administered or for how long, and the specific dosage of the botulinum toxin to use entail consideration of factors such as the patient's size, weight, age, and disease severity which factors are routine considerations determined on a patient by patient basis by the treating physician who has knowledge of the therapeutic use of a botulinum toxin."

These statements by the Brin declarant, an expert of long standing in the therapeutic use of botulinum toxin refute the assertion by the Office Action, through the making of a § 112(1) rejection, that the claimed method for treating bradycardia is not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Additionally, it is not correct that "a large degree of experimentation is necessary" (page 7 of the Office Action) to practise the claimed invention or that "the present invention is unpredictable" (page 8 of the Office Action) because: "it is reasonable to conclude...that for a patient with bradycardia, vagal nerve inhibition and hence an increase in heart rate can be accomplished by intrapericardial injection of a botulinum toxin to the SA node or to the AV node of the heart of a patient with bradycardia" (paragraph 15 of the Brin declaration).

Furthermore it is not true that "undue experimentation would be required of the skilled artisan to determine the optimal dose of botulinum toxin to be administered" (page 9 of the Office Action) because: "...matters such as the specific time period in which the toxin should be administered or for how long, and the specific dosage of the botulinum toxin to use entail consideration of factors such as the patient's size, weight, age, and disease severity which factors are routine considerations determined on a patient by patient basis by a cardiologist of ordinary skill who has knowledge of the therapeutic use of a botulinum toxin" (paragraph 16 of the Brin declaration).

Finally, the Office Action states that the claimed invention cannot be enabled because: (1) the art is contradictory and "...the heart is a complex organ and numerous challenges to botulinum toxin therapy have been reported (citing to the Johnson 1999 reference) (page 4 of the Office Action); (2) "The present invention is unpredictable and complex wherein on skilled in the art may not necessarily treat bradycardia by intrapericardial injection of a botulinum toxin to an SA node or AV node of a heart of a patient" (page 8 of the Office Action), and (3) "Although the complications observed by Lamanna arise after intravenous injection of botulinum toxin and administration of botulinum toxin to an isolated heart, similar problems may be possibly observed after intrapericardial injection of botulinum toxin to the SA node or AV node of the heart as claimed in the instant application." (page 11 of the Office Action).

All these statements and opinions by the Office Action are clearly wrong in light of the recent demonstration by medical researchers that *in vivo* administration of a botulinum toxin to the SA node of a mammals' heart does indeed treat bradycardia. See e.g. Masato T., et al., *Botulinum neurotoxin A blocks cholinergic ganglionic neurotransmission in the dog heart*, Jpn J Pharmacol 2002;89(3):249-254 (copy attached) wherein it was demonstrated

that administration of a botulinum toxin to the sinoatrial node of dog heart blocks parasympathetic (i.e. cholinergic) mediated bradycardia.

Note that the Brin declaration states at paragraph 15: "... I am in agreement with their conclusion (in the Masato publication) that this foreshadows clinical use of botulinum toxin to treat bradycardia, as set forth in this patent application."

The Brin declaration presents admissible expert opinion evidence which rebuts the *prima facie* case of lack of enablement made by the Office Action. Furthermore, the Masato publication shows that direct administration of a botulinum toxin to a mammal's heart can be used to treat bradycardia. For these reasons the § 112(1) rejection should be withdrawn.

III. The Section 112(2) Rejection

The rejection of claims 7, 15-17 and 36-38 by the Office Action under 35 U.S.C. §112, second paragraph has been overcome by spelling out the terms "SA" and "AV" in claim 1 and by changing "an" to "the" in claim 1, as suggested by the Office Action. Hence the rejection should be withdrawn.

Support for amending "SA" to "sinoatrial" can be found at at least page 1 ,line 19 of the specification. Support for amending "AV" to "atrioventricular" can be found at at least page 2, line 31, page 3, line 9, page 7, line 20 and page 8, line 30 of the specification.